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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,277	03/06/2002	Thomas Ehrhardt	50716	2896

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,277	EHRHARDT ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,10,14 and 19-23* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,14,22 and 23* is/are rejected.

7)☒ Claim(s) *19-20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Final Rejection

1. Applicants' amendment filed 7.24.2006 is acknowledged.

2. Claims 9-10, 14, 19-20 and new claims 21-23 are pending in this application.

3. **Claims remain withdrawn** :

New claim 21 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. New claim 21 is directed is direct to 'a method of screening herbicidally active substances ---using 'dihydroorotase or a protein having dihydroorotase activity', which does not require the DNA for its production, as required in the originally elected method claim. The invention of claim 1 is therefore distinct as not requiring the recombinant production of dihydroorotase as compared to the instantly prosecuted invention requiring the recombinant production of dihydroorotase.

4. Claims 9-10, 14, 19-20 and 22-23 are under consideration in this examination.

5. Applicant's arguments filed 7.24.2006 have been considered and not found to be persuasive. The reasons are discussed following the rejection(s).

6. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

7. Claim Rejections - 35 USC § 112, first paragraph (Enablement)

Claims 9-10, 14 & 22-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method (or process) for finding herbicidal active substances by inhibiting the activity of a plant dihydroorotase,

comprising producing dihydroorotase recombinantly using the DNA sequence of SEQ ID NO: 1, does not reasonably provide enablement for using any DNA sequence having at least 60% or 80% homology to SEQ ID NO: 1 or 'using **a** DNA sequence of SEQ ID NO: 1' which is interpreted here to mean a fragment of the DNA of SEQ ID NO: 1, and which encodes a protein having the enzymatic activity of a dihydroorotase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 9-10, 14 & 22-23 are so broad as to encompass a method of identifying an inhibitor of any dihydroorotase, which is encoded by a DNA having at least 60% or 80% identity to SEQ ID NO: 1. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of dihydroorotase broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequence of SEQ ID NO: 1 and encoded amino acid sequence of dihydroorotase of SEQ ID NO: 2.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions

or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of any dihydroorotase by modifying the DNA to have a homology of at least 60% or 80% to SEQ ID NO: 1, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting dihydroorotase activity; (B) the general tolerance of dihydroorotase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any dihydroorotase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including dihydroorotase with an enormous number of amino acid modifications of the of SEQ ID NO: 2 [as a result of modifying the DNA]. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of dihydroorotase(s) having

the desired biological characteristics, and further use in the method for identifying herbicidal compounds is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. *See* In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' arguments (previous):

Applicants point out that in addition to SEQ ID NO: 1 from *S. tuberosum*, on page 2, line 9, DHO from *A. thaliana* is disclosed and this can be used according to the present invention. One of ordinary skill in the art easily would be able to find other DHO sequences, for example from other plant species based on sequence similarity or mutagenesis techniques. Also, functionally unrelated DNA would not fall under the scope of present claim 9. Multienzyme DHO complexes such as those from yeast or *D. melanogaster* also would not be within the scope of claim 9 as they are not plants. DHO clearly is identified as an herbicide target.

Applicants also do not agree that the pending claims are directed to any DHO of certain homology, and the Applicants believe that screening for mutants DHO would be routine for one of ordinary skill in the art and can be done by *in vivo* mutagenesis. One of ordinary skill in the art would not have to undergo undue experimentation to obtain the modified DHO sequence[s]. Use of these sequences is illustrated in Greener et al. (1994).

In sum, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC 112, paragraph, because the claims clearly recite both structure and function.

Applicants' arguments have been considered and found to be persuasive, as far as the written description rejection is concerned, which rejection was hereby withdrawn.

However, Applicants' arguments with respect to the enablement rejection is not found to be persuasive because Applicants have clearly failed to address the key issues of the rejection. In particular the specification does not support the broad scope of the claims which encompass all modifications of any dihydroorotase by modifying the DNA to have a homology of at least 60% or 80% to SEQ ID NO: 1, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting dihydroorotase activity; (B) the general tolerance of dihydroorotase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any dihydroorotase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Also Applicants arguments that one of skill in the art can by *in vivo* mutagenesis to obtain modified sequences and with the aid of the works of Greener et al. use the sequences.

In response, Applicants do not explain how one of skill art will choose going about modifying the DNA sequences in order to encode a diverse range dihydroorotase, modified to the extent of 20-40%, which may be employed in the claimed method. Applicants present no details about the regions of dihydroorotase which can or cannot be modified because of the very nature of protein which may lead to an inactive protein. Thus leading to high

unpredictability. Details of other non-enabling factors are explained in the enablement rejection.

The reference of Greener has limited use and does not teach applicability to any gene, is time consuming and expensive and only limited number of random mutants can be generated (*see* page 32, column 1-2), as against modifying a sequence (SEQ ID NO: 1) by 20-40%. Applicants' new arguments are a newer version of the old arguments and are considered no different to the previous arguments. The rejection is therefore maintained.

8. Applicants' arguments (new):

Applicants argue that the instant specification provide specific guidance for the enablement of claims 9 & 14, and direct Examiner's attention to Example 2 of the specification fro recitation of comparisons of percentage identity of the protein of SEQ ID NO: 1 and various dihydroorotases.

In response, it is pointed out that SEQ ID NO: 1 is a nucleic acid sequence, not a protein sequence. It is however noted that Applicants' amino acid sequence of dihydroorotase of SEQ ID NO: 2 (from *Solanum tuberosum*) is 78% identical *Arabidopsis thaliana* dihydroorotase, 58% identical to *Synechocystic* dihydroorotase, and 55% identical to. *Coli* and *Pseudomonas putida* dihydroorotase. The above mentioned data is supplemented by Genbank accession numbers listed on page 2. Applicants argue that any reference known to one of ordinary skill in the art is allowed to show enablement. The Federal Circuit recently stated in *Falkner v. Inglis*, that "[a] patent need not teach, and preferably omits, what is well known in the art" (448 F.3d 1357 (Fed. Cir. 2006) (quoting *Spectra-Physics, Inc, v. Coherent, Inc., 827 F.2d* 1524, 1534 (Fed. Cir. 1987). *Falkner* acknowledges that coming of age of molecular biology by asserting that a

chemical structure required for a claim does not always have to be provided by a specification and in the application. Possession of such details can be imputed if shown in a publication before the filing date which, for example, is exemplified in this application by Zhou et al., Plant Physiol. 114: 1569 (1997). Accordingly, Applicants recitation of DNA sequence of SEQ ID NO: 1 or a DNA sequence having a homology of at least 60% with respect to SEQID NO: 1and which encodes a protein having dihydroorotase activity is enabled by the disclosure of the invention and the knowledge of one of ordinary skill in the art.

Applicants' arguments that *Falkner's* acknowledgement that "a chemical structure required for a claim does not always have to be provided by a specification and in the application", does not have any relevance to the instant situation because the instant claims under prosecution recite both structure and function. The key point at issue is whether sufficient guidance is provided by the instant specification or if sufficient guidance is provided to one skilled in the art to practice the claimed invention by modifying up to 20-40% of the sequence of the SEQ ID NO: 1. Such is not the case, because the mere knowledge of prior art sequences of dihydroorotase from other source of lesser homology is not guidance to manipulate the sequence of SEQ ID NO: 1 to the tune of 20-40%, which sequence can be modified by substitution, deletion, addition or insertion. Not a single mutant has been constructed nor a single amino acid has been modified as an example. SEQ ID NO: 2 is 346 amino acids in length. Modification of SEQ ID NO: 1 or encoded protein of SEQ ID NO: 2 by 20-40% will involve modification

ranging 69-138 amino acids of SEQ ID NO: 2, and such a modification is not enabled

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990. Science, Vol.247, pp.1306-1310, especially p.1306, column 2, paragraph 2). However, applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) with regard to the issue raised above.

Applicants' arguments that one of ordinary skill in the art can easily obtain mutation based on already known sequences such

as SEQ ID NO: 1, by *in vivo* mutagenesis, which is based upon the use of *E. coli* strains having mutations in the genes for the DNA repair system (e.g., Rupp, W. D. (1996), cited by Applicants) is considered but not found to be persuasive because of unpredictable nature in the mutation art and for reasons explained above.

Applicants further argue that the numerous Affymetrix patents clearly show that large scale screening was and is state of the art and comparison of a sufficient number of sequences of dihydroorotases to the disclosed dihydroorotase can be performed. However, Applicants failed to clearly show the relevance of excavating dihydroorotase sequences from the Web, as against modifying the dihydroorotase sequence in question to the extent of 20-40% in order to use it in the method claimed.

Applicants arguing the teachings of Greener et al. appear to think that the Examiner has repeatedly misinterpreted Greener et al. Applicants argue that the Examiner has failed to provide objective evidence. Applicants request an affidavit indicating the use of personal knowledge and allowance for Applicants to respond to the personal knowledge.

It is not clear what part of the 'Office Action' the Applicants consider as 'personal knowledge'. If Applicants consider 'common scientific knowledge' as 'personal knowledge', the Examiner will be glad to discuss the same, provided the specifics are known. If the Applicants are correct in there interpretation of the knowledge of the prior art it is not clear how the Applicants have not been able to address the key issues of the rejection. This rejection is not based upon one or more of the cited references, and must therefore be considered as a whole, including the factors addressed [*See* In re Wands 858 F.2d

731, 8 USPQ2nd 1400 (Fed. Cir, 1988)] in view of what is being claimed, the nature of invention and the state of the prior art. Therefore, what is presented here is a complete, objective and a clear analysis in the rejection and response to Applicants' arguments. The rejection is therefore maintained.

9. Claims 19-20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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